Journal of the Formosan Medical Association (2016) 115, 372–376

Available online at www.sciencedirect.com

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journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Herpes zoster could be an early manifestation of undiagnosed human immunodeficiency virus infection

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Received 16 May 2015; received in revised form 20 August 2015; accepted 21 August 2015

KEYWORDS
herpes zoster;
human immunodeficiency virus;
surveillance

Background/Purpose: No formal epidemiological research based on systematic analysis has focused on the relationship between herpes zoster and immunodeficiency virus (HIV) infection in Taiwan. Our aim was to explore whether herpes zoster is an early manifestation of undiagnosed human HIV infection in Taiwan.
Methods: This was a retrospective cohort study using the database of the Taiwan National Health Insurance Program. A total of 35,892 individuals aged ≤ 84 years with newly diagnosed herpes zoster from 1998 to 2010 were assigned to the herpes zoster group, whereas 143,568 sex-matched and age-matched, randomly selected individuals without herpes zoster served as the non-herpes zoster group. The incidence of HIV diagnosis at the end of 2011 was estimated in both groups. The multivariable Cox proportional hazards regression model was used to estimate the hazard ratio and 95% confidence interval (CI) for risk of HIV diagnosis associated with herpes zoster and other comorbidities including drug dependence and venereal diseases.
Results: The overall incidence of HIV diagnosis was 4.19-fold greater in the herpes zoster group than that in the non-herpes zoster group (3.33 per 10,000 person-years vs. 0.80 per 10,000 person-years, 95% CI 4.04–4.35). The multivariable Cox proportional hazards regression analysis revealed that the adjusted hazard ratio of HIV diagnosis was 4.37 (95% CI 3.10–6.15) for individuals with herpes zoster and without comorbidities, as compared with individuals without herpes zoster and without comorbidities.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2015.08.012

Conclusion: Herpes zoster is associated with HIV diagnosis. Patients who have risk behaviors of HIV infection should receive regular surveillance for undiagnosed HIV infection when they present with herpes zoster.

Introduction

Herpes zoster, commonly known as shingles, is caused by reactivation of latent varicella-zoster virus in the cranial-nerve or dorsal-root ganglia.[1,2] It is clinically characterized by painful grouped vesicles on a erythematous rash along the dermatome area, and it can result in chronic severe pain (postherpetic neuralgia), particularly in older people.[1–3] To date, multiple risk factors of herpes zoster have been well established, including immunosuppressive conditions, cancers, and chronic medical conditions.[3–6] In addition, a growing body of evidence reveals that the prevalence of human immunodeficiency virus (HIV) infection is considerably high among persons with high-risk behaviors presenting with herpes zoster.[7–9] Some studies have also revealed that herpes zoster could be an early manifestation of undiagnosed HIV infection because of an early defect in cell-mediated immunity.[9–12] In Taiwan, the first HIV patient was found in 1984, and at the end of 2013, the total number of HIV patients had reached 26,475.[13] To date, no formal epidemiological research based on systematic analysis has focused on the relationship between herpes zoster and HIV infection in Taiwan. If herpes zoster is really an early manifestation of undiagnosed HIV infection, patients with high-risk behaviors of HIV infection should undergo testing for undiagnosed HIV infection when they present with herpes zoster. Therefore, we conducted a population-based cohort study using the database of the Taiwan National Health Insurance Program to explore this issue.

Methods

Design and study population

This was a retrospective cohort study using the database of the Taiwan National Health Insurance Program. The program, which was implemented in March 1995, covers almost 99% of 23 million people living in Taiwan.[14] The details of the program have been well written in previous high-quality studies.[15–17] The study was approved by the Institutional Review Board of China Medical University and Hospital in Taichung, Taiwan (CMUH-104-REC2-115).

Study participants, comorbidities, and main outcome measurement

We identified individuals aged $\leq$ 84 years with newly diagnosed herpes zoster as the herpes zoster group from 1998 to 2010, based on the International Classification of Diseases, 9th Revision (ICD-9 code 053). The date of diagnosing herpes zoster was defined as the index date. Four folds of comparison individuals without herpes zoster were randomly selected from the same database to serve as the non-herpes zoster group. The non-herpes zoster participants were matched with the herpes zoster participants by sex, age (every 5-year span), comorbidities, and the index year of diagnosing herpes zoster. We excluded individuals with HIV diagnosis (ICD-9 codes 795.71, V08, 042, and 079.53) at the baseline in both groups. The following potential risk factors for HIV infection were used: drug dependence (ICD-9 code 304) and venereal diseases (ICD-9 codes 090—099). All study participants were followed until they were diagnosed with HIV infection or until the end of 2011.

Statistical analysis

The distributions of sex, age, and comorbidities were compared between the herpes zoster group and the non-herpes zoster group using the Chi-square test for categorized variables and *t* test for continuous variables. The incidence of HIV diagnosis was estimated as the number of HIV diagnosis event identified during the follow-up period, divided by the total follow-up person-years for each group. The multivariable Cox proportional hazards regression model was used to estimate the hazard ratio and 95% confidence interval (CI) for risk of HIV diagnosis associated with herpes zoster and other comorbidities. The proportional hazard model assumption was also examined using a test of scaled Schoenfeld residuals. In the model evaluating the risk of HIV diagnosis throughout overall follow-up period, results of the test revealed a significant relationship between Schoenfeld residuals for herpes zoster and follow-up period, suggesting that the proportionality assumption was violated ($p = 0.002$). In the subsequent analyses, we stratified the follow-up period to deal with the violation of proportional hazard assumption. The statistical significance level was set at two-sided $p < 0.05$. All analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of the study population

Table 1 shows the distributions of sex, age, and comorbidities between the herpes zoster group and the non-herpes zoster group. There were 35,892 individuals in the herpes zoster group and 143,568 individuals in the non-herpes zoster group, with similar distributions of sex and age. The mean ages (standard deviation) of the study participants were 51.6 $\pm$ 19.1 years for the herpes zoster group and 51.2 $\pm$ 19.2 years for the non-herpes zoster group. The

Table 1 Characteristics of the herpes zoster group and the non-herpes zoster group.

Characteristic	Non-herpes zoster $N = 143,568$	Herpes zoster $N = 35,892$	p[a]
Sex			0.99
Male	68,424 (47.7)	17,106 (47.7)	
Female	75,144 (52.3)	18,786 (52.3)	
Age group (y)			0.99
<20	11,398 (7.9)	2848 (7.9)	
20–39	26,321 (18.3)	6577 (18.3)	
40–64	65,774 (45.8)	16,447 (45.8)	
65–84	40,080 (27.9)	10,020 (27.9)	
Age (y), mean (SD) [b]	51.2 (19.2)	51.6 (19.1)	<0.001
Baseline comorbidities			
Drug dependence	161 (0.11)	31 (0.09)	0.18
Venereal diseases	222 (0.15)	66 (0.18)	0.22

SD = standard deviation.
Data are presented as *n* (%) unless otherwise indicated.
[a] Chi-square test, comparing participants with and without herpes zoster.
[b] *t* test, comparing participants with and without herpes zoster.

proportions of drug dependence and venereal diseases were equally distributed in both groups.

Incidence of HIV diagnosis in the study population

The follow-up results revealed that the overall incidence of HIV diagnosis was 4.19-fold greater in the herpes zoster group than that in the non-herpes zoster group (3.33 per 10,000 person-years vs. 0.80 per 10,000 person-years, 95% CI 4.04–4.35). The incidence rates of HIV diagnosis, as stratified by sex, age, and follow-up period, were all higher in the herpes zoster group than those in the non-herpes zoster group. Most new HIV diagnosis occurred in male individuals. The incidence rate of HIV diagnosis was higher in male participants than in female participants in both groups. The herpes zoster group aged 20–39 years had the highest incidence rate of HIV diagnosis (8.56 per 10,000 person-years). The analysis stratified by follow-up period revealed that the risk of HIV diagnosis persisted over time, even after 1 year of diagnosing herpes zoster. However, the risk appeared much higher during the 1-year follow-up period, and was particularly highest in the first 3 months with an incidence rate ratio of 14.0 (95% CI 13.3–14.8; Table 2).

HIV diagnosis associated with herpes zoster and other comorbidities

Drug dependence and venereal diseases were included as comorbidities. The multivariable Cox proportional hazards regression analysis revealed that the adjusted hazard ratio of HIV diagnosis was 4.37 (95% CI 3.10–6.15) for individuals with herpes zoster and without comorbidities, as compared with individuals without herpes zoster and without comorbidities (Table 3).

The number needed to screen for HIV diagnosis

Table 4 shows that the number needed to screen for HIV diagnosis was 520.2 (35,892/69) for the whole herpes zoster group. In particular, the number needed to screen decreased to 99 among male participants aged 21–30 years.

Table 2 Incidence density of human immunodeficiency virus diagnosis in the herpes zoster group and the non-herpes zoster group.

	Non-herpes zoster				Herpes zoster				IRR (95% CI)[b]
	N	Event	Person-years	Rate[a]	N	Event	Person-years	Rate[a]	
All	143,568	66	829,723	0.80	35,892	69	206,906	3.33	4.19 (4.04–4.35)
Sex									
Male	68,424	56	390,349	1.43	17,106	61	97,337	6.27	4.37 (4.15–4.60)
Female	75,144	10	439,374	0.23	18,786	8	109,569	0.73	3.21 (3.03–3.39)
Age group (y)									
<20	11,398	8	76,621	1.04	2848	2	19,130	1.05	1.00 (0.85–1.18)
20–39	26,321	32	157,304	2.03	6577	34	39,708	8.56	4.21 (3.88–4.57)
40–64	65,774	19	384,302	0.49	16,447	27	95,352	2.83	5.73 (5.41–6.06)
65–84	40,080	7	211,495	0.33	10,020	6	52,716	1.14	3.44 (3.19–3.71)
Follow-up period									
≤3 mo	143,568	2	35,825	0.56	35,892	7	8951	7.82	14.0 (13.3–14.8)
3–12 mo	142,990	5	106,325	0.47	35,709	16	26,539	6.03	12.8 (12.2–13.4)
1–3 y	139,734	23	244,931	0.94	34,862	28	61,051	4.59	4.88 (4.70–5.08)
>3 y	105,888	36	442,643	0.81	26,389	18	110,366	1.63	2.01 (1.91–2.10)

CI = confidence interval; IRR = incidence rate ratio.
[a] Incidence rate: per 10,000 person-years.
[b] IRR: herpes zoster versus non-herpes zoster (95% CI).

Table 3 Cox proportional hazards regression analysis for risk of human immunodeficiency virus diagnosis associated with herpes zoster and comorbidities.

Variable		Event	Person-years	Rate[a]	Adjusted HR[b] (95% CI)
Herpes zoster	Comorbidities[c]				
No	No	63	827,943	0.76	1 (Reference)
No	Yes	3	1780	16.9	21.2 (6.65–67.7)
Yes	No	68	206,375	3.29	4.37 (3.10–6.15)
Yes	Yes	1	531	18.8	24.0 (3.34–172.9)

95% CI = 95% confidence interval; HR = hazard ratio.
[a] Incidence rate: per 10,000 person-years.
[b] Adjusted for sex and age.
[c] Comorbidities including drug dependence and venereal diseases.

Discussion

In this retrospective cohort study, we observed that the overall incidence of HIV diagnosis was 4.19-fold greater in the herpes zoster group than that in the non-herpes zoster group. We also observed that patients with herpes zoster were associated with 4.37-fold increased risk of HIV diagnosis. In this study, because we selected patients with herpes zoster prior to the confirmed diagnosis of HIV, herpes zoster really preceded the serological detection of HIV. Some studies have revealed that herpes zoster in areas with high prevalence of HIV infection has an approximately 90% positive predictive value for underlying HIV infection.[11,18,19] Previous studies have established an increased risk of herpes zoster among HIV-infected patients.[20,21] This risk can be reduced by highly active antiretroviral therapy, but remains three times higher than that found in the HIV-negative population.[21,22] Therefore, our findings suggest that herpes zoster could be an early manifestation of undiagnosed HIV infection in Taiwan, which is compatible with the results of previous studies.[9–12] We observed that most new HIV diagnosis occurred in male participants (Table 2). As shown in Table 4, among 61 male patients with HIV diagnosis in the herpes zoster group, 47 male patients were aged 11–50 years (77%). We also observed that the risk of HIV diagnosis appeared much higher during the 1-year follow-up period, and is particularly high during the first 3 months (incidence rate ratio 14.0; Table 2). These findings highlight that patients who have risk behaviors of HIV infection should undergo tests for serological detection of HIV when they present with herpes zoster, particularly for younger male patients within 1 year of being diagnosed with herpes zoster.

Several important limitations of this study should be discussed. First, owing to the inherent limitation, some risk behaviors of HIV infection, such as history of injection drug use and history of sexual contact, were not recorded in this database. Therefore, we used drug dependence as an alternative variable instead of injection drug use and venereal diseases as an alternative variable instead of a history of sexual contact. Second, because of the same limitation, whether patients had other symptoms or signs potentially related to HIV infection other than herpes zoster cannot be determined in this study. Third, we observed that the risk of HIV diagnosis persisted over time, even up to 3 years after the diagnosis of herpes zoster. Whether the persistent risk is caused by risk behaviors introduced after herpes zoster was diagnosed or by the latent status of HIV

Table 4 Number needed to screen (NNS) for human immunodeficiency virus diagnosis.

	Herpes zoster (N = 35,892)						p[b]
	Female			Male			
	N	HIV diagnosis	NNS	N	HIV diagnosis	NNS	
Overall[a]	18,786	8	2348.3	17,106	61	280.4	<0.001
Age group (y)							
1–10 (N = 592)	300	0	—	292	0	—	—
11–20 (N = 2256)	969	0	—	1287	2	643.5	0.22
21–30 (N = 3051)	1467	1	1467	1584	16	99	<0.001
31–40 (N = 3526)	1736	1	1736	1790	16	111.9	<0.001
41–50 (N = 5486)	3010	2	1505	2476	13	190.5	0.001
51–60 (N = 7793)	4542	2	2271	3251	7	464.4	0.03
61–70 (N = 6402)	3491	2	1745.5	2911	6	485.2	0.09
71–80 (N = 5402)	2631	0	—	2771	1	2771	0.33
>80 (N = 1384)	640	0	—	744	0	—	—

[a] Overall NNS = 520.2 (35,892/69).
[b] Fisher's exact test, comparing male and female participants.

infection cannot be determined in this observational study. Fourth, surveillance bias could be another possible explanation for the association between herpes zoster and HIV diagnosis. For example, patients with herpes zoster are more likely to be screened and further to be identified for their HIV diagnosis. Fifth, the number needed to screen for HIV diagnosis was 520.2 in this study. The number needed to screen decreased to 99 among male patients aged 21—30 years. In fact, not all herpes zoster patients need to be screened for HIV diagnosis. Only those who have risk behaviors of HIV infection should receive screening for undiagnosed HIV infection when they present with herpes zoster. Therefore, clinicians should collect complete histories, such as history of injecting drug use and history of sexual contact, to clarify whether patients with herpes zoster are at an increased risk of HIV infection, particularly among younger male patients. If clinicians can focus on patients with risk behaviors, the number needed to screen can be reduced.

In spite of the above-mentioned limitations, this study was also noted to have several strengths. This is the first population-based cohort study to explore the relationship between herpes zoster and HIV diagnosis in Taiwan. This study included a large sample size with long-term follow-up period to increase its statistical power. It provides updated information on herpes zoster and HIV diagnosis. We conclude that herpes zoster is associated with HIV diagnosis. Herpes zoster could be an early and clinically detectable manifestation of undiagnosed HIV infection in Taiwan. Patients who have risk behaviors of HIV infection should receive regular surveillance for undiagnosed HIV infection when they present with herpes zoster, particularly younger male patients within 1 year of being diagnosed with herpes zoster.

Acknowledgments

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002), China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092),National Research Program for Biopharmaceuticals (NRPB) Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006), Tseng-Lien Lin Foundation in Taichung, Taiwan, Taiwan Brain Disease Foundation in Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds in Japan. These funding agencies did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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